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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/623,611	Applicant(s) COIA ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003 and 09 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *22-27 and 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,28 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 5/9/03 (Paper No. 23), is acknowledged.
Claims 1-33 *are pending.*

2. Applicant's election with traverse of Group I and species elections of somatostatin, human antibodies, and V86 in Paper No. 20 is acknowledged. The traversal is on the grounds that unity of invention exists because Group I does define a contribution over the prior art. This is not found persuasive for the reasons provided in detail in the discussion of Applicant's comments with respect to Peach et al. in the rejection set forth under 35 USC 102.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-27 and 29-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20.

Claims 1-21, 28 and 33 *are under consideration in the instant application.*

Sequence Compliance

3. Sequence compliance: Applicant's amendment, filed 5/9/03, adding sequence identifiers to the brief Description of Figure 6 is acknowledged. Applicant's comment that the sequence identifiers are for sequences present in the Sequence Listing and CRF filed 7/19/02 are also acknowledged. Accordingly, the instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Drawings

4. The drawings submitted 2/3/03 have been approved by the Draftsman.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

IDS

6. Applicant's IDSs, filed 9/5/2000 and 12/12/2002 (Paper Nos. 1.5 and 18), are acknowledged. Copies of these 1449s indicating consideration of the cited references were attached to Paper No. 19.

Specification

7. The Abstract provided 10/6/2000 is objected to for the following informalities:
Applicant should avoid the use of novel in the abstract, as patents are presumed to be novel and unobvious.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Claim Objections

9. Claim 19 is objected to for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

10. Claim 33 is objected to because of the following informalities: claim 33 is dependent on a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112 second paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10, 13-21, 28 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-10, 13-21, 28 and 33 are ambiguous in their recitation, either directly or via their dependency, of a "V-like domain (VLD) derived from a non-antibody ligand".

It is acknowledged that the specification on page 5 at lines 25-30 disclose that a VLD is a domain which has structural features *similar to* the variable heavy or variable light domains of an antibody, including the CDR loop structures, but is neither an antibody nor a TcR. However, the metes and bounds of this limitation are unclear at least in that Table 1 on page 6 indicates that VLD derived from non-antibody ligands includes proteins which have a "C domain" but not a "V domain" (e.g., CD16 and CD19 in Table 1). Thus it is unclear if the term "VLD" is limited to only those domains considered to be "V domains" in the art, or if it also encompasses any domain that might be broadly construed to be a "V-like domain" by some undefined criteria.

B) Claim 21 recites the limitation "or multivalent reagent according to claim 1" in the preamble. There is insufficient antecedent basis for this limitation in the claim because claim 1 recites only a binding moiety.

It is suggested that Applicant either amend claim 21 to depend from claim 1 or claim 20 in the alternative, or to delete the reference to a multivalent reagent.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-10, 13-21, 28 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite a "V-like domain (VLD) derived from a non-antibody ligand" as part of the invention.

The specification discloses on page 5 at lines 25-30 that a "V-like domain (VLD) derived from a non-antibody ligand" is any domain which has a structure *similar* to an antibody heavy or light chain variable region, and which features CDR loop structures which are surface loop structures *like* those of antibody CDRs. The bridging paragraph of pages 5-6 of the specification discloses that a "non-antibody ligand" is *any* ligand which binds a specific binding partner and which is not an antibody or T cell receptor (TcR). .

The claims are not limited to binding moieties which share a *single* "V-like domain derived from a non-antibody ligand" as a structural basis (i.e., a "scaffold") to which modifications of the loops are made to provide binding of target molecules of interest. Instead, the claims are drawn to a genus of "binding moieties" structures which comprise *any* protein domain which can be considered by ambiguous criteria to be a "V-like domain", so long as the "V-like domain" is not derived from an antibody or TcR (i.e., is "derived from a non-antibody ligand").

The genus of structures encompassed by the instant claims is large, particularly since the metes and bounds of domains that constitute a "V-like domain" are unclear and the negative limitation that the "V-like domain" not be derived from an antibody or TcR does not provide a positive description of what actually IS encompassed within the genus.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

In the instant case the specification provides binding moieties comprising a single species of monomeric V-like domain derived from a non-antibody ligand: the V domain derived from the non-antibody ligand CTLA-4. While Table 1 does suggest other sources of "V-like domains", no evidence is provided that any of the domains of any of the molecules set forth in Table 1 would function as a "binding moiety". Neither does the specification appear to describe what particular aspects of the CTLA4 V domain structure correlate with the observed function of a "binding moiety"; thus Applicant does not appear to have described a correlation between a particular structure and the claimed function that can be generalized to other "V-like domains derived from non-antibody ligands" to show that Applicant was in possession of the generic invention.

In view of the single species described which functions as a "binding moiety", the lack of an adequate description of what aspects of the structure of that single species are shared by members of the genus to provide the binding function, and the lack of clear metes and bounds of the claimed genus in view of Applicant's definitions; the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

15. Claims 1-10, 13-21, 28 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a binding moiety comprising the V domain of CTLA-4 in which one or more CDR loop structures has been modified or replaced with a polypeptide which has a binding affinity for a target molecule of interest, does not reasonably provide enablement for binding moieties comprising any "V-like domain from a non-antibody ligand". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the instant claims encompasses a protein which can function as a "binding moiety" for any target sequence of interest and which shares at least one monomeric "V-like domain (VLD) derived from a non-antibody ligand".

The specification discloses on page 5 at lines 25-30 that a V-like domain is a domain which has a structure *similar* to an antibody heavy or light chain variable region, and which features CDR loop structures which are surface loop structures *like* those of antibody CDRs. The bridging paragraph of pages 5-6 of the specification discloses that a "non-antibody ligand" is any ligand which binds a specific binding partner and which is not an antibody or TcR. Examples of "non-antibody ligands" which provide "V-like domains" are provided in Table 1.

The claims are not limited to binding moieties which share a particular "V-like domain". Instead the claims encompass any non-antibody/non-TcR protein domain which can be broadly characterized as a "V-like domain" in which loop structures of the domain can be modified or replaced to result in affinity for a target molecule of interest, so long as certain other wished for criteria are met and the scaffold is not derived from an antibody or TcR.

As noted supra the scope of the instant claim is unclear because the definitions provided in the specification create ambiguity as to the metes and bounds of a "V-like domain derived from a non-antibody ligand".

Even were the claims limited to a V domain (as opposed to a "V-like" domain), it would still be unpredictable which V domains could be used as a scaffold to provide a binding moiety as currently recited. Although V domains do share certain basic structural features, there is variation in details of the structures that makes it unpredictable for a given V domain whether it would function as a scaffold, particularly in monomeric form, without actually testing that particular V domain.

The specification provides a single working example of a V domain that can serve as such a scaffold – the V domain of CTLA4. From results in this one working example, Applicant generalizes the observations with the CTLA4 V domain scaffold to encompass any binding domain in which a "V-like domain" is used as a scaffold. Metzler et al. (Nat. Structural Biol. 1997; 4(7):527-531) teach that the structure of CTLA-4 is distinct from that usually found in IgSF V domain in that the beta sheet surface is atypically flat (e.g. page 529). Bajorath (J. Mol. Model 1999; 5:169-170) teaches that the V domain of ICOS, one of the proteins in the same family as CTLA-4, has a non-conserved B-C loop compared to CTLA-4 (page 173), has an alternate glycosylation site in what in CTLA-4 is the ligand binding site (page 174), and in addition has other differences including loss of the A-strand conserved in other V domains (e.g., page 173). The skilled artisan would thus consider it unpredictable as to whether even a monomeric V domain from ICOS, a member of the same family as CTLA-4, could be used like CTLA-4 as a scaffold for producing a binding moiety.

The instant claims recite those characteristics observed with respect to the CTLA-4 scaffold that Applicant chose to test. However, the specification does not appear to provide guidance as to how to *predict* which other V domains or V-like domains are likely to have these recited attributes observed for the particular V domain found in CTLA4. Thus the instant claims are essentially a "wish to know" the identity of other monomeric V-like domains derived from non-antibody ligands that could function as a scaffold for insertion of target-binding sequences to form the instantly claimed "binding moiety". It has been previously decided that claims recitations so broad do not provide sufficient guidance as to how to make and use the claimed invention. See Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Without guidance as to which particular V domains derived from non-antibody ligands other than CTLA- to select as likely to have the desired properties of being a monomer with increased solubility relative to the wildtype and tolerant to loop substitution, it would require undue experimentation of the skilled artisan to screen V domains from any of the large number of members of the Ig superfamily which have V domains or "V-like domains" at random and hope that another besides CTLA-4 could be identified.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance as to which properties of V domains are necessary for monomer formation and tolerance to loop substitution, the identity of those particular "monomeric V-like domains derived from a non-antibody ligand" could be used to form a binding moiety as broadly as now claimed is unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

16. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 28 recites a pharmaceutical composition comprising a binding moiety. Claiming a "pharmaceutical composition" (in contrast to a composition in a pharmaceutically acceptable carrier) requires that the composition have an in vivo function.

Although Applicant has provided working examples showing that a binding moiety comprising a CTLA-4 scaffold in which somatostatin and other peptides were inserted would bind the various corresponding targets, the specification appears to provide insufficient guidance that any particular binding moiety could be used as a pharmaceutical composition. There does not appear to be any in vivo data provided showing that a binding moiety comprising a CTLA-4 (or any other) V-like domain could function in vivo.

Pharmaceutical therapies in the absence of *in vivo* data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Given the technical difficulties associated with *in vivo* therapies and the insufficient guidance provided in the specification as filed, the skilled artisan would be faced with undue experimentation in determining which binding moieties could be utilized *in vivo*.

Claim Rejections – 35 U.S.C. § 102

17. In view of the linking status of claim 1, the following rejections are set forth with respect to the enabled breadth of the linking claim and claims which depend therefrom.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

19. Claims 1, 7, 10-11, 13, 20, 21, 28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Peach et al. (J. Exp. Med. 1994; 180:2049-2058, IDS # AE, see entire document).

Applicant's arguments, filed 2/3/03, and arguing that the instant claims contribute a contribution over the teachings of Peach et al. have been fully considered as they apply to the instant rejection but have not been found convincing for the reasons set forth below.

Peach et al. teach chimeric molecules in which complementarity determining regions (CDRs) of CD28 and CTLA4 have been exchanged (see entire document, especially Table 2). Both CTLA4 and CD28 are T cell surface proteins that are non-antibody ligands comprising at least one monomeric V-like domain. Peach et al. show in Figure 4 that chimeric proteins such as HS4, HS4A, HS7, HS8, HS10, HS11, HS12 and HS13 each exist in monomeric form. The dimeric form of each chimeric molecule is also a "multivalent reagent comprising two or more binding moieties".

Peach et al. teach that the binding affinity of at least some of these chimeric proteins is altered for B7-1 compared to the parent molecules (e.g., page 2052-2053). In addition, the chimeric proteins of Peach et al. each are a "binding moiety" since they bind monoclonal antibodies to CD28 (e.g., page 2052, bridging paragraph).

Although Peach et al. are silent with respect to the effect of these changes in the CDR loop structures on solubility, Peach et al. also show in Figure 4 that chimeric proteins HS10, HS11, HS12 and HS13 each exist in monomeric form at a greater frequency than do either CD28 or CTLA4. Thus Figure 4 provides objective evidence that at least the chimeric proteins HS4, HS4-A, HS7, HS8, HS10, HS11, HS12 and HS13 have improved solubility when compared with the unmodified VLDs of CD28 and CTLA4.

Applicant argues that Peach et al. do not teach the reader to modify CDR structures within a monomeric V-like domain in order to increase the solubility of the domain.

However, the instant claims are not method claims and although the reasons for producing the product may be different from that of the instant Inventors, there is no requirement that the prior art appreciate the properties inherent to the product.

Applicant further argues that the binding domains taught by Peach et al. are fusion proteins, and suggests that the fused Ig constant domain is needed to achieve solubility.

The Examiner again acknowledges that the chimeric proteins are fusion proteins. However, the "comprising" language of the claims encompasses fusion proteins. Further it is noted that in Figure 4 all of the proteins, including the wildtype CD28 and CTLA4 proteins, are evaluated in fusion protein form. Thus the increase in the lower molecule weight band corresponding to monomer in the above noted constructs reflects an effect of the CDR loop modification.

Applicant further questions whether the lower molecular weight bands are in fact monomers, noting that the gel is of immunoprecipitated material, that the arrows marking the position of CD28Ig and CTLA4Ig monomers does not correspond to any of the lower molecular weight bands, and that Peach et al. do not describe these forms as "monomers", but rather only as "additional species".

The Examiner acknowledges that the gel of Figure 4 is of material immunoprecipitated prior to loading and that aggregates would be lost. However, the appearance of any monomer, particular relative to the level of dimer, must necessarily indicate that there was overall a shift in equilibrium towards the monomer form relative to the unmodified molecules shown in the left lanes. The Examiner further notes that the immunoprecipitation step results in both monomeric and a multivalent form (i.e., the dimeric chimeric proteins) immobilized on a solid support, as recited in claim 21.

It is also acknowledged that the arrows on the left side of the gel marking the position of CD28Ig and CTLA4Ig monomers does not correspond in size with the bands that the Examiner has argued are monomeric chimeric proteins. However, on page 2052 Peach et al. point out that the chimeric proteins migrate at a position between that of CD28Ig and CTLA4Ig; thus it is not surprising that monomeric forms of the chimeric proteins should be found between the markers for monomers of CD28Ig and CTLA4Ig. It is further noted that a fair reading of the bridging paragraph on page 2052 is that Peach et al. DO consider these "additional species" to be monomers, particularly since all of the chimeric proteins migrate between the position of CD28Ig and CTLA4Ig when all proteins are subjected to SDS-PAGE under reducing conditions.

Applicant further argues that even if the chimeric proteins of Figure 4 of Peach et al. are monomers, the teachings of Peach et al. still do not anticipate the instant claims because Peach et al. do not appreciate that modifications of the CDR loops can improve folding and/or reduce aggregation of monomeric V-like domains.

However, it is again noted that the instant claims are not a method of making and there is no requirement that Peach et al. appreciate any of the properties inherent in the molecules described. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. In the instant case the chimeric molecules of Peach et al. appear to meet the instant claim limitations. As long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999).

It is further noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113. Thus claim 33 is also anticipated.

Finally, Peach et al. teach the chimeric proteins are expressed in COS cell supernatants, which since they are taken from growing cells must be considered a pharmaceutically acceptable carrier or diluent. Applicant is reminded that a "pharmaceutical composition" is claiming in terns of intended use, and the claim reads on the ingredients.

The reference teachings thus anticipate the instant claimed invention.

20. Claims 1-9, 13, 15-16, 18-19, 21, 28 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Koide (US 2003/0134386, see entire document).

Koide teaches and claims binding polypeptides which use Fn3 as a scaffold (see entire document, *including claims*).

Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules).

Koide teaches and claims that the loop region can vary from the wildtype FN3 loop by the insertion of from two to 25 amino acids (e.g., claim 5).

Koide teaches that the Fn3-based binding polypeptides are useful as artificial mini-antibodies whose small size and single domain structure avoid some of the problems of antibodies while allowing binding to a variety of molecular structures for therapeutic, diagnostic and catalytic applications (see especially paragraphs 1-21 ad 94-99).

Koide et al. teaches that the loops of the Fn3 domain can be replaced with loop structures derived from antibodies, including the mouse antibody D1.3(e.g., paragraphs 105-136).

Koide does not teach that the solubility of the modified Fn3 domain is improved compared to the unmodified Fn3 domain, but improvement of solubility would be inherent in at least some of the constructs of Table 1.

Similarly, although not explicitly taught, deletion of the RGD sequence of the Fn3 FG loop as taught in Table 1 would necessarily reduce the affinity of the modified loop to at least one natural ligand (e.g., the integrin $\alpha 5\beta 1$, see paragraph 98)

Koide does teach that the modified Fn3 domain have a binding specificity different than the unmodified domain because binding of HEL is taught in Figures 9 and 10 for the target ubiquitin and in the Examples IX-XIII at paragraphs 171-188).

Koide also teaches replacement of a loop structure with a binding determinant from a non-antibody polypeptide since the randomized sequence inserted for the library that yielded the ubiquitin-specific domain may be considered a "non-antibody polypeptide" (see paragraphs 160-170 for libraries with non-antibody loops and paragraphs 177-180 for the production of the ubiquitin-binding polypeptide).

Labeling of the binding polypeptides with a diagnostic reagent that is a radioisotope is taught at paragraph 135. Coupling of the binding polypeptides to a solid support occurs during the panning steps of the library amplification and selection since the binding polypeptide expressed by the phage is bound to the target coupled to a dish (e.g., see paragraph 144).

Applicant is reminded that a "pharmaceutical composition" is claiming in terms of intended use, and the claim reads on the ingredients. Koide teaches compositions comprising the binding domains in pharmaceutically acceptable carriers such as PBS/EDTA at numerous locations (see for example paragraph 115).

It is further noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113. Thus claim 33 is also anticipated.

The reference teachings thus anticipate the instant claimed invention.

21. Claims 1-21, 28 and 33 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Nuttall et al. (PROTEINS: Structure, Function , and Genetics 1999; 36:217-227) creates an ambiguity regarding the contribution of Gregory Coia and Maria Galanis to the instantly claimed invention.

The Nuttall et al. paper overlaps extensively, but not completely, with respect to the teachings it provides compared to the instantly claimed invention. However, listed Inventors Coia and Galanis only appear in the acknowledgements section of the Nuttall et al. paper on page 226 as having provided "advice and helpful discussion".

Applicant is requested to clarify the contribution of each named Inventor to the instant Invention.

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (US 2003/0134386) in view of Bogden et al. (US Pat. No. 5,504,069).

The claims are drawn to a binding moiety comprising at least one monomeric V-like domain derived from a non-antibody ligand wherein at least one CDR loop structure or part thereof is replaced with a binding determinant derived from somatostatin.

The teachings of Koide have been discussed in full supra and teach a binding polypeptide Fn3 as a scaffold (see entire document, *including claims*). Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules).

Koide does not teach replacement of at least on CDR loop structure or a part thereof with a binding determinant derived from somatostatin.

However, Bogden et al. teach that somatostatin agonists were highly desirable for methods including the inhibition of trauma-induced tumor growth (see entire document). Bogden et al. teach that native somatostatin has a very short half-life in vivo because the peptide is rapidly inactivated by endo- and exopeptidases; thus agonists which maintain the function of somatostatin but remain active for longer periods were highly desirable (e.g., see column 4 at lines 35-67). Bogden et al. review that it was well known in the art at the time the invention was made that the somatostatin peptide could be modified in multiple ways to provide new structures that preserved the function of binding somatostatin receptors (see e.g., columns 5-8).

In view of the teachings of Koide that polypeptides of 2-25 amino acids can be inserted into the FG loop of FN3 to produce a binding polypeptide and the fact that somatostatin is a peptide within this size range; it would have been obvious to the ordinary artisan at the time the invention was made to insert somatostatin into the FG loop of the FN3 scaffold taught by Koide. The ordinary artisan would have been motivated to insert somatostatin into the FG loop of the Fn3 scaffold in order to provide an agonist of somatostatin function of sufficient stability and size such that it would not be readily cleaved by endo- or exopeptidases, and could therefore remain active longer in vivo than the unmodified somatostatin peptide.

In view of the teachings of Koide regarding methods of modifying the Fn3 scaffold by inserting peptides into the FG loop, and the teachings in the art with respect to the production of agonists using the somatostatin peptide sequence, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing an Fn3 scaffold having the FG loop replaced by somatostatin, and that the chimeric polypeptide would still bind somatostatin receptors. An increase in solubility compared to the unmodified Fn3 domain would be an expected outcome of inserting the longer somatostatin peptide into the FG loop. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

24. Claims 1 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (US 2003/0134386) in view of Cai et al. (Proc. Natl. Acad. Sci. USA 1996; 93:6280-6285).

The claims are drawn to a binding moiety comprising at least one monomeric V-like domain derived from a non-antibody ligand wherein one or more CDR loop structures are replaced with one or more CDR loop structures derived from the human anti-melanoma antibody V86.

The teachings of Koide have been discussed in full supra and teach a binding polypeptide Fn3 as a scaffold (see entire document, *including claims*). Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules). Koide teaches that the Fn3-based binding polypeptides are useful as artificial mini-antibodies whose small size and single domain structure avoid some of the problems of antibodies while allowing binding to a variety of molecular structures for therapeutic, diagnostic and catalytic applications (see especially paragraphs 1-21 ad 94-99).

Koide et al. teaches that the loops of the Fn3 domain can be replaced with loop structures derived from antibodies, including the mouse antibody D1.3(e.g., paragraphs 105-136).

Koide does not teach replacement of one or more CDR loop structures with one or more CDR loop structures derived from the human anti-melanoma antibody V86

However, Cai et al. teach the human anti-melanoma antibody V86 (see entire document). Cai et al. teach that unlike most antibodies, the specificity of V86 is contained within the VH domain since a full VL domain is not expressed by V86 (e.g., summarized in Abstract). Cai et al. note the art-recognized applications of anti-melanoma antibodies as immunodiagnostic reagents (e.g., page 6280 introduction). Cai et al. teach the amino acid sequence of the V86 antibody (see Table 1).

In view of the teachings of Koide that CDR loops from different antibodies could be used to replace the corresponding loops of the Fn3 domain and yield a binding polypeptide with the specificity of the donor antibody; it would have been obvious to the ordinary artisan at the time the invention was made to replace the corresponding loops of the Fn3 scaffold taught by Koide with the CDRs of the V86 VH domain. The ordinary artisan would have been motivated to make such a replacement because, as taught by Koide, binding polypeptides using the Fn3 scaffold avoid certain problems associated with antibodies.

In view of the teachings of Koide regarding methods of modifying the Fn3 scaffold by replacing Fn3 loops with CDRs from an antibody, and the teachings in the art with respect to the V86 CDR sequences, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing an Fn3 scaffold having the CDRs of V86, and that the chimeric polypeptide would still bind the melanoma antigen bound by V86. An increase in solubility compared to the unmodified Fn3 domain would be an expected outcome of replacing the Fn3 loops with the V86 CDRs. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

25. No claim is allowed.

26. Applicant Note: A declaration under 37 CFR 1.131 or 1.132 would not be sufficient to overcome the rejection of the instant claims as being anticipated by or obvious over Koide (US 2003/013386). See 37 C.F.R 1.608(b).

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for before Final submissions is (703) 872-9306.

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